EXHIBIT #55D

esis of both psychiatric disorders and VVS [5–8], it is still unclear whether VVS causes psychiatric morbidity or the psychiatric substrate predisposes to syncopal events. These issues are further obscured since the prevalence and mechanism of syncope in patients with MPDs has not been fully assessed.

In the present study, we tested the hypothesis that MPDs are associated with increased excitability of the vasovagal reflex and predispose to VVS. For this reason, we assessed the prevalence of syncope and the response to head-up tilt test (HUTT) in patients with recently diagnosed MPDs. We also assessed the efficacy of psychiatric treatment in reducing the recurrence of syncopal episodes in patients with MPDs and history of syncope.

Methods

In a prospective cohort analysis among 627 patients referred to the Psychiatric Outpatients Department between years 2003 and 2005, we studied 82 patients with recently diagnosed MPDs (DSM-IV-TR™ criteria) [9]. They were not under any psychiatric treatment nor had ever been treated before. The diagnosis of MPD was established within 1 month before inclusion in the study, after psychiatric interview based on SCID [10]. MPDs included: (a) mood disorder (minor depressive disorder that did not fulfill the criteria for dysthymia or major depressive episode), and (b) anxiety disorders (panic and generalized anxiety disorder).

During the initial evaluation, cardiologic, neurological, hormonal and biochemical tests were normal, ruling out other causes of syncope [11, 12]. Quality of life was assessed by means of the Short-Form Health Survey questionnaire [13, 14]. All patients were asked to report (a) any history of syncope in lifetime and (b) the number of their syncopal episodes during the last 12 months, as suggested by the European Society of Cardiology and the American College of Cardiology [15, 16]. Then, they underwent a HUTT with clomipramine, according to the previously described protocol [8, 15, 17].

The response to HUTT and the number of reported syncopal events were compared between the MPD group, a group of age- and sex-matched patients of equal age with documented recurrent VVS (5 VVS episodes in lifetime and at least 2 episodes during the last year), who were also untreated when initially evaluated (VVS group) and a third group of matched healthy volunteers (control group). Both cardiologists and psychiatrists who performed HUTTs and clinical interviews were blind to each other's diagnosis.

After the initial evaluation, patients of the MPD group were treated with antidepressants (fluoxetine 20 mg or sertraline 100 mg daily), benzodiazepines (alprazolam 1 mg daily) or the combination of both, as indicated [18–20]. During treatment, they were asked to report any syncopal episode. At the end of a 12-month follow-up period, they underwent a final cardiologic and psychiatric evaluation, and quality of life reassessment.

Patients in the VVS group were treated with general measures of syncope avoidance (such as salt and water intake, early recognition of prodromal symptoms and sitting or lying down to avoid falls). Fifteen of them were adjunctively administered fluoxetine (20 mg daily) due to recurrence of syncope during follow-up [15].

The study protocol was approved by the ethics committee of the hospital, and all subjects enrolled gave their informed consent. We used Yates corrected χ^2 analysis to compare the prevalence of syncope and the rate of positive HUTT among groups. ANOVA was used to compare syncopal episodes and quality of life prior to and following therapy. Values are expressed as mean ± 1 standard deviation. A p value <0.05 was considered statistically significant.

Table 1. History of syncope and rate of positive HUTT

	Groups		
	MPD (n = 67)	VVS (n = 67)	controls (n = 67)
Patients with syncope	30 (45%)*,#	67 (100%)*	0 (0%)
Patients with positive HUTT	39 (58%)*,#	57 (85%)*	3 (5%)

* $p < 0.01$ compared to controls; # $p < 0.01$ compared to VVS group.

Results

Out of the 82 initially evaluated patients with MPDs, 5 refused psychiatric therapy (3 with anxiety, 2 with mood disorders) and 10 did not comply with the follow-up schedule (6 with anxiety, 4 with mood disorders).

Among the remaining 67 patients (mean age 42 ± 18, 38 men), 42 had anxiety and 25 mood disorders. None of them fulfilled the criteria for other axis I or for axis II disorders. Thirty of these 67 patients (45%) had a history of syncopal episodes in their lifetime. The number of their syncopal events during the last 12 months before treatment was 2.5 ± 1.4. More than half of the patients in the MPD group (39/67, 58%) had a positive HUTT, according to the criteria of the European Task Force on Syncope and the American College of Cardiology [1, 15, 21]. This proportion was lower than that in the VVS group ($p < 0.01$), but significantly higher than in normal controls (table 1).

Among the 30 patients with a history of syncope, the rate of positive HUTT was even higher (25/30, 83%) and comparable to that observed in the VVS group (85%). However, even in patients with MPDs who had not experienced syncope, the rate of positive HUTT was higher than in the control group (14/37, 38%, $p < 0.01$).

Table 2. Quality of life parameters in psychiatric patients (mean ± 1 SD)

SF-36 score	Patients with syncope			Patients without syncope		
	before therapy	after therapy	p	before therapy	after therapy	p
Physical function	74 ± 4	83 ± 4	NS	73 ± 5	82 ± 5	NS
Role physical	46 ± 7	79 ± 7	0.002	46 ± 8	76 ± 9	0.01
Role emotional	49 ± 7	71 ± 6	0.04	50 ± 8	69 ± 8	NS
Social function	51 ± 3	55 ± 3	NS	51 ± 3	55 ± 3	NS
Mental health	59 ± 4	68 ± 4	NS	60 ± 5	66 ± 5	NS
Vitality	50 ± 4	59 ± 4	NS	52 ± 5	57 ± 5	NS
Bodily pain	77 ± 4	90 ± 3	0.02	76 ± 5	88 ± 5	0.05
General health	59 ± 5	68 ± 5	NS	60 ± 6	66 ± 7	NS
Health changes	39 ± 4	64 ± 4	0.0005	39 ± 4	64 ± 5	0.0003

SF-36 = Short-Form Health Survey questionnaire.

During follow-up, 37 patients with MPDs were treated with benzodiazepines, 20 with SSRIs, and 10 with the combination of both drugs. After treatment, only 6 of the 30 patients with MPDs and syncopal episodes experienced syncope recurrence ($p < 0.01$). No difference in therapeutic efficacy was observed between benzodiazepines, SSRIs, and combined treatment. Psychiatric drug treatment resulted in a significant decrease in the number of syncopal episodes (from 2.5 ± 1.4 before treatment to 0.6 ± 0.5 during treatment, $p < 0.01$), in a pattern similar to that observed in VVS patients following treatment (from 2.7 ± 1.3 to 0.7 ± 0.5, respectively).

In patients with MPDs and history of syncope, the decrease in the number of syncopal spells came along with improvement in psychiatric symptoms, as evaluated by the final psychiatric interview. Additionally, a significant improvement in the quality of life score was observed, as shown in table 2. An identical improvement in quality of life was also observed in psychiatric patients without syncopal episodes.

Discussion

The main findings of the present prospective, controlled study are as follows: (a) Patients with MPDs had an increased rate of positive response to HUTT, as compared to normal controls. This high rate was observed in both patients with and without a history of syncope. (b) The high rate of positive HUTT was associated with a high incidence of syncopal episodes in patients with MPDs. The proportion of positive HUTT among those patients with MPDs who also had experienced syncopal events was almost as high as that observed in patients with recurrent VVS. (c) Psychiatric drug treatment decreased the occurrence of syncope and was associated with improvement in patients' psychiatric symptoms and quality of life. These results imply a close relationship between psychiatric substrate and vasovagal physiology.

The association between VVS and psychiatric disorders, though not fully elucidated, has been known for many years [22–24]. Panic disorder has been associated with autonomic dysreactivity [25–30]. It has also been reported that panic symptoms reappear in 42% of patients after hyperventilation, a maneuver that has been associated with the vasovagal reflex [31–34]. Besides, mental stress and particular emotional states facilitate or trigger syncopal episodes in patients with VVS [3, 15]. The prevalence of anxiety and mood disorders in patients with VVS may be as high as 26% [4, 35]. Despite these observations, it is not clear whether psychiatric disorders are consequent to recurrent syncope, or whether they predispose to syncopal episodes. In our study, the increased excitability of the vasovagal reflex observed in the MPD group was associated with increased prevalence of syncope, implying the vasovagal origin of fainting.

In accordance with our findings, an exaggerated drop in cerebral blood flow has been reported in patients with panic disorder, similar to that observed in patients with VVS [25, 36–38]. A predominant vagal activity has also been observed in patients with blood phobia [39]. On the other hand, there are studies disputing the role of parasympathetic response in patients with panic disorder, while sympathetic predominance has also been reported in these patients [39, 40]. However, sympathetic dominance may precede sympathetic withdrawal, leading to syncope, similarly to what happens in the Bezold-Jarisch reflex [37]. Different patterns of autonomic balance may not only explain the variety of symptoms observed in anxiety disorders, but also suggest the presence of a neurally mediated mechanism of syncope in heterogenic psychiatric populations, as in our case [41, 42].

In our study, a parallel improvement in psychiatric symptoms, quality of life, and recurrence of syncope was observed following psychiatric drug treatment. This finding is in accordance with our previous observation that fluoxetine may be effective in improving quality of life and symptoms in some patients with VVS [43]. Benzodiazepines have also been therapeutically used in VVS [1, 15]. The effect of these drugs might be attributed to the improvement of a subthreshold psychiatric disorder. However, in patients with MPDs and history of syncopal events, the effect of psychiatric drug treatment or psychotherapy on syncope recurrence has not been systematically assessed. The therapeutic benefits of psychotherapy in anxiety and mood disorders are well known. It may also prove efficient in patients with concomitant VVS, as it is the case with pharmacotherapy. The experience of psychotherapy in patients with recurrent VVS is also limited and mainly concerns desensitization or cognitive behavioral therapy [44, 45]. Although a variety of therapeutic means have been used in VVS, not one of them was effective enough to be widely applied. Therefore, our findings appear to be of clinical value, since the diagnosis and treatment of underlying MPDs, when present, may be crucial for the effective treatment of VVS. This approach may be more important for patients with certain emotional triggers of syncope, such as blood-injury phobia [44]. Besides, in patients with MPDs a considerable part of syncopal events should not be regarded as 'psychogenic pseudosyncope' but as true syncope with an underlying vasovagal mechanism [35].

In conclusion, MPDs were associated with increased excitability of the vasovagal reflex and a relatively high incidence of syncopal episodes. Improvement in psychiatric symptoms following pharmacotherapy was associated with significant decrease in syncope recurrence, independent of the drug being used. These findings suggest involvement of co-occurring MPDs in the pathogenesis of VVS.

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a small study of individualized stress management for patients with hypertension showed improvement in blood pressure as a result of the intervention, with reduction in blood pressure correlated with reduced stress and improved coping with anger.

SYNCOPE

Definition and Comparative Nosology

Syncope is defined as a sudden, transient loss of consciousness with associated loss of postural tone, followed by spontaneous recovery, and is due to temporary reduction of cerebral blood flow. A recent report of long-term follow-up from the Framingham Heart Study found the incidence of first report of syncope to be 6.2 cases per 1,000 person-years. Approximately 3 percent of emergency room visits and 1 to 6 percent of hospital admissions are for syncope. Mechanisms of syncope include disruption in vascular tone or inadequate blood volume, heart rhythm disorders, perfusion failure in aortic stenosis or severe pulmonary hypertension, or primary cerebrovascular insufficiency (usually vertebrobasilar insufficiency). Disruption in autonomic tone is most common, and vasovagal syncope, also referred to as *vasodepressor* or *neurocardiogenic syncope*, and postural hypotension account for 30 to 50 percent of all cases of syncope. Syncope can occur as a single episode or can be recurrent and chronic. Approximately 30 to 40 percent of syncope is idiopathic. It is most important to detect bradyarrhythmias and ventricular tachyarrhythmias as an underlying cause, because these are usually associated with underlying structural heart disease and carry increased mortality risk.

Diagnosis and Clinical Features

Physical examination, including supine and standing blood pressure, and ECG are the basic examinations for patients with syncope. Abnormal ECG or structural heart disease often dictates stress testing, echocardiography, ambulatory monitoring, or electrophysiological (EP) study. In the absence of structural heart disease, the most likely cause of syncope is one of the neurally mediated syndromes. Tilt testing with or without isoproterenol infusion or sublingual nitroglycerine helps demonstrate orthostatic hypotension and neurocardiogenic syncope, but results of tilt testing are often irreproducible, and specificity and sensitivity of tilt testing are disappointing.

Differential Diagnosis

Drop attacks, dizziness, and vertigo do not cause loss of consciousness. Seizures can be difficult to distinguish from syncope, but a preceding aura, prolonged loss of consciousness for more than 5 minutes, and rhythmic movements during loss of consciousness are characteristic of seizures. Precipitating pain, micturition, defecation, exercise, or stress is associated with syncope rather than seizures.

Course and Prognosis

Heart disease is an important prognostic indicator in syncope. In particular, patients with syncope with associated left ventricular dysfunction and CHF have significant 1-year mortality risk. Older age, ventricular arrhythmias, abnormal ECG, and heart failure contribute additive mortality risk in syncope patients. Long-term follow-up data indicate no increase in mortality or MI risk for patients with vasovagal syncope or orthostatic hypotension but increased risk of death and MI for patients with syncope due to underlying hea neurological disease, or syncope of unknown cause.

Treatment

Treatment addresses the underlying cause of syncope. w ble. For the majority of patients with idiopathic syncope cardiogenic syncope, orthostatic hypotension, or vasovaga or a combination of these, behavioral interventions inclu tion about avoiding precipitants and lying down when pı symptoms arise. Alcohol consumption, sleep deprivation, i hydration, and prolonged standing should be avoided.

β-Blockers and β-adrenergic agonists have been used f cological treatment of syncope, but clinical trials are lacki shown at best equivocal efficacy. Permanent pacemakers best option for patients with recurrent syncope with signif tional impairment, particularly if bradycardia has been de by cardiac monitoring or tilt testing.

Psychological Factors Affecting Syncope

Although anxiety and acute emotional stress are recognize itants of syncope, the prevalence of these factors in syncope Anxiety and panic disorder are common in patients with rec cope, but whether they were present before syncope or on not been well established. One recent study found no dif tween syncope patients with and without positive tilt table t of panic and generalized anxiety disorder, but identified de a predictor of recurrent syncope over 3-year follow-up. I noted that some clinicians distinguish *hysterical fainting* cope by the absence of pallor, hypotension, or bradycardia hysterical faint, but the prevalence of this condition and i ship to psychological factors or psychiatric diagnoses are

CONGENITAL HEART DISEASE

Congenital heart defects occur in 1 percent of live birth past 25 years, advances in cardiac surgery have enabled p would previously have died in childhood to reach adultl of these patients have residual abnormalities of circulat uncorrected problems or to surgical modification of circu complications include right to left shunts with cyanosis, si node dysfunction, arrhythmias, heart block, valvular dysfu risk of endocarditis. Ventricular dysfunction can also occu or left heart failure. Adjustment and developmental probl to be common in patients with congenital heart disease.

VALVULAR HEART DISEASE

The relationship between valvular heart disease and psyc order has been a matter of considerable interest over the decades. In panic disorder, mitral valve prolapse is detec 25 percent of patients studied with echocardiography. Ho lapse also occurs in a substantial portion of the populat panic disorder, and the nature of the relationship remain The subjective experience of valve prolapse (e.g., flutterir pressure) may be a trigger for panic sensations; alternative ciation may be purely coincidental. Obsessive-compulsi (OCDs), tic disorders, and Tourette's syndrome are asso poststreptococcal immune system–mediated inflammator that are similar to those leading to glomerulonephritis an

Vascular Laboratory

BOSS, LARRY - 000346448320

* Final Report *

Result Type:	Vascular Laboratory
Result Date:	30 September 2009 0:00
Result Status:	Authenticated
Result Title:	Vascular Lab Report
Performed By:	Contributor_system, SOFTMED on 30 September 2009 0:00
Verified By:	Contributor_system, SOFTMED on 30 September 2009 0:00
Encounter info:	000212495824, NMH, Outpatient, 9/30/2009 - 9/30/2009

* Final Report *

Vascular Lab Report

NORTHWESTERN MEMORIAL HOSPITAL
VASCULAR LAB REPORT
(312) 926-2746
DATE: 09/30/2009

NAME:	Boss, Larry	HOSPITAL #:	00034644-8320
TEST PHYSICIAN:	William Pearce, MD, RPVI	BILLING #:	000212495824
REFERRING MD:	Mark Morasch, MD, RPVI	PATIENT LOC:	OUTP000000
PAT. TYPE:	O	DISCH DATE:	

CAROTID AND VERTEBRAL DUPLEX EXAM

Reason for Exam: Carotid artery disease.

RIGHT
The common and internal carotid arteries have soft, smooth plaque with a less than 60% diameter reduction.
The external carotid artery is normal.
The right ICA peak systolic velocity is 93 cm/sec and the end diastolic velocity is 27 cm/sec.

LEFT
The common carotid artery has soft, smooth plaque with a less than 60% diameter reduction.
The external and internal carotid arteries are normal.
The left ICA peak systolic velocity is 121 cm/sec and the end diastolic velocity is 31 cm/sec on the left.

The vertebral and subclavian arteries are within normal limits bilaterally.

DIAGNOSTIC IMPRESSION:
Hemodynamically insignificant bilateral common carotid artery and right internal carotid artery disease. The Vascular Laboratory velocity criteria used to quantitate the degree of carotid stenosis was established based on comparison to angiography using the NASCET criteria comparing the highest degree of stenosis with the diameter of the distal ICA.

Printed by: Dinkins, Dorothy
Printed on: 1/22/2010 13:41

JAN-22-2010 15:15 From:312 926 3050

... in women and probably from seizure [illegible]. In addition, ictal masturbation has [illegible] woman with nymphomania proved to have [illegible] sensory simple partial seizures caused [illegible] representing her genital region.

Suicide. The risk of completed suicide [illegible] four to five times greater than that [illegible] tion, and those with complex partial seizures [illegible] have a particularly high risk [illegible] suicide occurs in 3 to 7 percent of epileptic [illegible] suicide attempts among patients with epilepsy [illegible] ... nonepileptic controls [illegible] with epilepsy had attempted suicide [illegible] controls. This increased risk of suicide [illegible] poral lobectomy and successful control [illegible] behavior among epileptic patients [illegible] the psychosocial stressors of having [illegible] patients are likely to attempt suicide [illegible] personality behaviors and are likely [illegible] ictal psychosis. Contributors to [illegible] hallucinations, agitated compulsion [illegible] sional ictal command hallucinations [illegible]

A 26-year-old woman had her initial [illegible] at 18 years of age. Her seizures [illegible] in a cave," a motionless stare [illegible]

[illegible] and toxicology screens used [illegible] tests are useful [illegible] the most widely used confir- [illegible] are frequently normal [illegible] maneuvers, such [illegible] for an extended period [illegible] activity. Neuroimaging proce- [illegible] imaging (MRI), can [illegible] or even mesial temporal scle- [illegible] surgically and in localizing the [illegible] (SPECT) scans, and PET scans [illegible] around the tempo- [illegible] in the presurgical assessment of [illegible] Neuropsychological examina- [illegible] further help in localizing and [illegible] surgery.

[illegible] in epilepsy are mediobasal tem- [illegible] of epileptic adults have [illegible] of these have mesial temporal [illegible] hippocampus. Theories about [illegible] include perinatal insults, dys- [illegible] Another 20 to 25 percent [illegible] have tumors, such as hamartomas and gangliogliomas. The rest have scars from trauma and other causes or lack a distinct histological lesion.

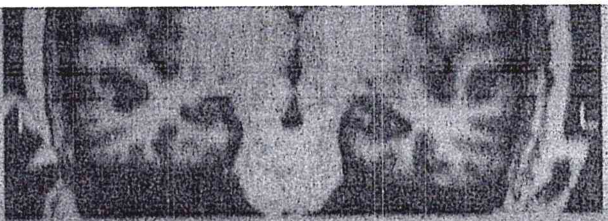

FIGURE 2.4-4. A series of magnetic resonance imaging scans demonstrating mesial-temporal sclerotic changes in the left hippocampal region. (From Engel J Jr. In vivo imaging the temporal lobe limbic system. In: Trimble MR, Bolwig TG, eds. *The Temporal Lobes and the Limbic System.* Petersfield, UK: Wrightson Biomedical Publishing; 1992, with permission.)

DIFFERENTIAL DIAGNOSIS

atonic = lack of normal tone
ictus = a blow, attack, stroke

Clinicians must distinguish epileptic seizures from two other transient behavioral events, syncope and nonepileptic seizures (pseudoseizures). *Syncope* is a loss of consciousness, usually with premonitory lightheadedness, autonomic reactivity, a brief atonic ictus, and little or no postictal confusion. Syncope lacks the many characteristic features of seizures and a clear epileptiform EEG. *Nonepileptic seizures*, on the other hand, are involuntary, psychogenically induced spells that, by definition, mimic many epileptic behaviors.

Differentiating epileptic seizures from nonepileptic seizures can be extremely difficult, and even epileptologists are incorrect 20 to

October 27, 2010

To Whom It May Concern:

Mr. Larry Boss is a 58 year old man I began to see in individual out-patient psychotherapy on January 14, 2010. He suffers with a Generalized Anxiety Disorder (300.02). This condition has persisted for over two years and is related to a stressful work situation. His psychological condition has become complicated by intensification of the restlessness, sleep disturbance, fatigue, concentration difficulties, nausea, and periodic bouts of syncope. Additionally, his psychological disorder complicates, and is further complicated by, his Diabetes Mellitus. There is no illicit drug, alcohol, anti-social, or malingering problem.

I recommend that he be granted an extended medical leave of absence.

Sincerely,

Robert A. Fajardo, M.D.